PATENT ABSTRACTS OF JAPAN

(11) Publication number : 06-100464
(43) Date of publication of application : 12.04.1994

(51) Int. Cl. A61K 37/30
A61K 37/30
A61K 9/14
A61K 47/18
A61K 47/26
A61K 47/36

(21) Application number : 04-147121
(22) Date of filing : 08.06.1992

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(54) COMPOSITION OF CALCITONINS FOR TRANSPULMONARY ADMINISTRATION

(57) Abstract:
PURPOSE: To obtain a powder composition for transpulmonary administration, capable of efficiently absorbing a calcitonin from alveolar mucosa, having excellent stability of active ingredient because of powder preparation, consequently enabling practical use of administration agent substituting an injection of a calcitonin.
CONSTITUTION: A powdery composition for transpulmonary administration comprises a powdery calcitonin and at least a water-soluble base, has 60% or more particle size distribution of particles having ·10 micron average particle diameter of the composition.

LEGAL STATUS

[Date of request for examination]	21.12.1998
[Date of sending the examiner's decision of rejection]	12.11.2002
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]	
[Date of final disposal for application]	
[Patent number]	
[Date of registration]	
[Number of appeal against examiner's decision of rejection]	
[Date of requesting appeal against examiner's decision of rejection]	
[Date of extinction of right]	

CLAIMS

[Claim(s)]
[Claim 1] The powder constituent for transpulmonary administration of calcitonins with which calcitonins are made into an active principle, and a water-soluble basis is contained at least, and particle distribution of the mean particle diameter of this constituent of 10 microns or less is characterized by being powdered at 60% or more.
[Claim 2] The powder constituent for transpulmonary administration according to claim 1 which is one sort chosen from the group which a water-soluble basis becomes from water-soluble saccharide, dextrins, and amino acid, or two sorts or more.
[Claim 3] The powder constituent for transpulmonary administration according to claim 1 in which calcitonins come to carry out 0.1-100 unit content per 1mg of these constituents.

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TECHNICAL FIELD

[Industrial Application] This invention makes calcitonins an active principle, contains a water-soluble basis at least, and particle distribution of the mean particle diameter of this constituent of 10 microns or less is 60% or more, and it relates to the powder constituent for transpulmonary administration of the calcitonins characterized by the powdered thing.

[Translation done.]

PRIOR ART

[Description of the Prior Art] Generally calcitonins are known in the bioactive peptide used as a current remedy as peptide hormone which has a serum calcium phosphoric-acid lowering operation and osteoclasis depressant action, and an antiulcer action. Clinically, it is used as a remedy to various hypercalcemias and a Paget's disease of bone, and osteoporosis. However, since calcitonin is a hydrophilic property and is a peptide whose molecular weight is about about 3,400, and membrane permeability is easy to be understood within an alimentary canal by the enzyme again low, it is known for internal use that it is very difficult to make the inside of the body absorb.
[0003] Therefore, it has been conventionally restricted to hypodermically, the intramuscular injection, and the intravenous injection. However, although many medication methods, such as a nose, the rectum, lungs, a vagina, an eye, tunica mucosa oris, and the skin, were tried since injection was accompanied by pain, there was a problem by decomposition by membrane permeability and the proteolytic enzyme etc.

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EFFECT OF THE INVENTION

[Effect of the Invention] The powder constituent for transpulmonary administration of the calcitonins of this invention can be easy, and can make insurance absorb calcitonins efficiently from alveolus membrane. Moreover, since it is powder pharmaceutical preparation, it excels in the stability of an active principle. Therefore, by this invention, utilization of the administration agent which changes to the injections of calcitonins was attained.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention makes calcitonins an active principle, contains a water-soluble basis at least, and particle distribution of the mean particle diameter of this constituent of 10 microns or less is 60% or more, and it relates to the powder constituent for transpulmonary administration of the calcitonins characterized by the powdered thing.
[0002]
[Description of the Prior Art] Generally calcitonins are known in the bioactive peptide used as a current remedy as peptide hormone which has a serum calcium phosphoric-acid lowering operation and osteoclasis depressant action, and an antiulcer action. Clinically, it is used as a remedy to various hypercalcemias and a Paget's disease of bone, and osteoporosis. However, since calcitonin is a hydrophilic property and is a peptide whose molecular weight is about about 3,400, and membrane permeability is easy to be understood within an alimentary canal by the enzyme again low, it is known for internal use that it is very difficult to make the inside of the body absorb.
[0003] Therefore, it has been conventionally restricted to hypodermically, the intramuscular injection, and the intravenous injection. However, although many medication methods, such as a nose, the rectum, lungs, a vagina, an eye, tunica mucosa oris, and the skin, were tried since injection was accompanied by pain, there was a problem by decomposition by membrane permeability and the proteolytic enzyme etc.
[0004]
[Problem(s) to be Solved by the Invention] On the other hand, the aerosol for lung absorption which used propellants for calcitonin is proposed (JP,60-161924,A). Since it is the cause which destroys earth environment by being discarded in atmospheric air in order that these propellants may generally use comparatively the liquefaction hydrocarbon fluoride (chlorofluocarbon) which is inert gas by low toxicity, the activity of chlorofluocarbon tends to provide homogeneity with the powder constituent for transpulmonary administration of suitable calcitonins preferably at an alveolus rather than calcitonins are absorbed safely and efficiently moreover by carrying out inhalation administration, without using chlorofluocarbon there.
[0005]
[Means for Solving the Problem] Then, it found out that calcitonins absorbed from transpulmonary administration to the whole body efficiently by the artificers of this invention being more simple without using propellants like chlorofluocarbon, and preventing adhesion of the calcitonins in the pharynx section, and pulverizing the constituent of the mixture which contains the water-soluble basis containing calcitonins as a result of inquiring wholeheartedly about the administration pharmaceutical form of the calcitonins for transpulmonary administration which effectiveness discovers certainly to 10 microns or less.
[0006] It was completed based on the above-mentioned knowledge, and this invention makes calcitonins an active principle, contains a water-soluble basis at least, and particle distribution of the mean particle diameter of this constituent of 10 microns or less is 60% or more, and it is the powder constituent for transpulmonary administration of the calcitonins characterized by the powdered thing.
[0007] Generally the calcitonins which are the active principle of this invention are known as polypeptide hormone which has a serum calcium phosphoric-acid lowering operation and osteoclasis depressant action, and an antiulcer action. Clinically, it is used as a remedy to various hypercalcemias and a Paget's disease of bone, and osteoporosis. The natural mold or the derivative by composition is known by calcitonins. As an example of natural mold calcitonin, eel calcitonin, calcitonin salmon, Swine calcitonin, Homo sapiens calcitonin, fowl calcitonin, etc. are mentioned. As synthetic calcitonin It is the derivative of natural mold calcitonin which permuted the 1.7th place of a disulfide bond by the ethylenic linkage in the amino suberic acid suitably. For example, [ASU1.7] eel calcitonin (WHO, a generic name: elcatonin), [ASU1.7] calcitonin salmon, [ASU1.7] fowl calcitonin, or [ASU1.7] Homo sapiens calcitonin is mentioned. Especially elcatonin is most suitable calcitonin used by this invention.
[0008] As a water-soluble basis used for this invention, it is water-soluble saccharide, dextrins, and amino acid. Although monosaccharide, disaccharide, and polysaccharide are mentioned as a saccharide, it is D-mannitol, grape

sugar, a lactose, fruit sugar, trehalose, an inositol, and cane sugar preferably, and the dextrins as polysaccharide are desirable and alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin, etc. are mentioned. A glycine, a taurine, etc. are mentioned as amino acid.

[0009] freeze drying and mixing with well-known preparation of the powder constituent for transpulmonary administration of this invention, and grinding -- ********** -- things are made.

[0010] For example, in order to obtain the powder constituent for transpulmonary administration of uniform calcitonin, calcitonins [minute amount / effective dose] and a water-soluble basis are once dissolved in distilled water, and it freeze-dries, and considers as a solid-state, and in order to pulverize further, it can prepare to impalpable powder using a ball mill grinder and a jet mill grinder. Moreover, it can prepare in target concentration and a target amount by adding and carrying out preferential grinding of the extending agent of an initial complement to a freeze-dried object if needed.

[0011] Furthermore, as for the particle diameter of the powder constituent for transpulmonary administration of this invention, it is desirable that particle size distribution 10 microns or less are 60% or more. In 10 microns or more, it adheres to a bronchial tube etc., without arriving to an alveolus, even if it inhales, and the absorption coefficient of calcitonin falls. Therefore, particle at least 10 microns or less of the constituent of this invention is 75% or more preferably 60% or more.

[0012] What is necessary is to be 0.1 units / mg - 100 unit / concentration of mg generally, to be one unit - 50 unit / mg preferably as concentration of the calcitonins in the constituent of this invention, to take the concentration of these calcitonins into consideration and just to adjust combination to calcitonins and a water-soluble basis.

[0013] Moreover, 1 time of the dose of the powder constituent for transpulmonary administration of this invention has desirable 10-100mg as a constituent, and 1 - 3 times is suitable for the count of administration on the 1st. Calcitonins can be made to absorb from lungs efficiently by the approach of it not being limited especially as the transpulmonary administration approach in this constituent, and filling up a capsule with a constituent, for example, equipping an inhaler (spin spatula -) at the time of an activity, and inhaling a constituent in lungs.

[0014]

[Example] Although an example and the example of an experiment are given to below and this invention is explained in more detail, this invention is not limited to this.

[0015]

[Example 1] Elcatonin 40mg and 2g of D-mannitol were taken to the beaker, and after adding 50ml of distilled water and dissolving, the freeze-dried powder which freeze-dries a solution, grinds with a mortar and contains uniform elcatonin 100 unit / mg was obtained. Thus, 1.2g of freeze-dried powder and 28.8g of D-mannitol containing elcatonin 100 acquired unit / mg were often mixed, and it pulverized using the jet mill (Powrex make). Thus, the obtained powder pharmaceutical preparation was prepared as dry powder - which carried out the 4.5 units (actual measurement by liquid chromatography) / mg content of the elcatonin. As a result of measuring the particle size distribution of the powder constituent for transpulmonary administration prepared as this dry powder - with a particle-size-distribution measuring device (SACT-2: Shimadzu), they were 10-20-micron 5-10-micron 61.6% 5 microns or less, and 13.4%, and 4.0%, and 21.0% 20 microns or more.

[0016] Experiment 1: Transpulmonary administration (n=3-4) of dry powder - containing elcatonin 4.5 unit prepared in the example 1 / mg was carried out to lungs in 15 units / Kg, 30 units / Kg, and 75 units / Kg pressure type in spatula - under [part / which was exposed / rat tracheotomy] effect pentobarbital anesthesia of calcium concentration in blood after the transpulmonary administration of the elcatonin in an animal experiment (a) rat. It collected blood every 4 hours and the calcium concentration in blood was measured for after [administration before administration] 30 minutes, 1 hour, 2 hours, and 3 hours.

(b) The result of having measured the calcium concentration in blood after result elcatonin transpulmonary administration was shown in drawing 1 (an axis of ordinate shows the calcium concentration (mg/dl) in blood, and an axis of abscissa shows the time amount after administration (Hr)). the dose of the powder constituent for transpulmonary administration of this invention becomes high with 15 units (- shows among drawing), 30 units (** shows among drawing), and 75 units (** shows among drawing) a passage clear from this drawing 1 -- alike -- following -- a dosage -- lowering of the calcium concentration in blood after administration is observed anaclitic, and it is shown that elcatonin was absorbed more efficiently than lungs so that clearly from drawing 1 .

[0017]

[Example 2] Elcatonin 40mg and trehalose 2g were taken to the beaker, and after adding 50ml of distilled water and dissolving, the freeze-dried powder which freeze-dries a solution, grinds with a mortar and contains uniform elcatonin 100 unit / mg was obtained. Thus, 1.2g of freeze-dried powder containing elcatonin 100 acquired unit / mg and the powder which often mixed trehalose 28.8g were pulverized using the jet mill (Powrex make). Thus, the obtained constituent was prepared as a powder constituent for transpulmonary administration of dry powder - which carried out the 4.3 units / mg content of the elcatonin (particle size distribution; 10-20-micron 5-10-micron 65.4% 5 microns or less, and 16.6%, and 5.3%, 12.7% 20 microns or more). Subsequently, the pharmaceutical preparation which contains elcatonin 100 unit per capsule can be obtained by filling up a No. 2 capsule with obtained 24mg dry

powder -. Furthermore, an inhalator (spin spatula -) is equipped with the capsule, and it can be certainly sprayed on human lungs.
[0018]
[Example 3] Elcatonin 40mg and glycine 2g were taken to the beaker, and after adding 50ml of distilled water and dissolving, the freeze-dried powder which freeze-dries a solution, grinds with a mortar and contains uniform elcatonin 100 unit / mg was obtained. Thus, 1.2g of freeze-dried powder containing elcatonin 100 acquired unit / mg and the powder which often mixed glycine 28.8g were pulverized using the jet mill (Powrex make). Thus, the obtained constituent was prepared as a powder constituent for transpulmonary administration of dry powder - which carried out 4 units / mg content of the elcatonin (particle size distribution; 10-20-micron 5-10-micron 54.4% 5 microns or less, and 20.8%, and 8.2%, 16.4% 20 microns or more).
[0019]
[Example 4] Elcatonin 40mg and glycine 2g were taken to the beaker, and after adding 50ml of distilled water and dissolving, the freeze-dried powder which freeze-dries a solution, grinds with a mortar and contains uniform elcatonin 100 unit / mg was obtained. Thus, 2.4g of freeze-dried powder containing elcatonin 100 acquired unit / mg and the powder which often mixed glycine 27.6g were pulverized using the jet mill (Powrex make). Thus, the obtained constituent was prepared as a powder constituent for transpulmonary administration of dry powder - which carried out 8 units / mg content of the elcatonin (particle size distribution; 5-10-micron 66.9% 5 microns or less, and 15.3%, more than 10-20 microns 10.2 or 20 micron 7.6 %). Subsequently, the pharmaceutical preparation which contains elcatonin 200 unit per capsule can be obtained by filling up a No. 2 capsule with this 25mg dry powder -. Furthermore, an inhalator (spin spatula -) is equipped with the capsule, and it can be certainly sprayed on human lungs.
[0020]
[Example 5] Synthetic calcitonin salmon 134mg and 2g of D-mannitol were taken to the beaker, and after adding 50ml of distilled water and dissolving, the freeze-dried powder which freeze-dries a solution, grinds with a mortar and contains uniform synthetic calcitonin salmon 200 unit / mg was obtained. Thus, 1.2g of freeze-dried powder containing synthetic calcitonin salmon 200 acquired unit / mg and the powder which often mixed 28.8g of D-mannitol were pulverized using the jet mill (Powrex make). Thus, the obtained constituent was prepared as a powder constituent for transpulmonary administration of dry powder - which carried out 8 units / mg content of the synthetic calcitonin salmon (particle size distribution; 5-10-micron 57.3% 5 microns or less, and 18.6%, 13.9% 10-20 microns 10.2 or 20 microns or more). Subsequently, the pharmaceutical preparation which contains synthetic calcitonin salmon 200 unit per capsule can be obtained by filling up a No. 2 capsule with this 25mg dry powder -. Furthermore, an inhalator (spin spatula -) is equipped with the capsule, and it can be certainly sprayed on human lungs.
[0021]
[Effect of the Invention] The powder constituent for transpulmonary administration of the calcitonins of this invention can be easy, and can make insurance absorb calcitonins efficiently from alveolus membrane. Moreover, since it is powder pharmaceutical preparation, it excels in the stability of an active principle. Therefore, by this invention, utilization of the administration agent which changes to the injections of calcitonins was attained.
[0022]

[Translation done.]